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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/520,489	03/08/00	TSCHOPP J	A049 US

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EXAMINER	
CANELLA,K	
ART UNIT	**PAPER NUMBER**
1642	6

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/520,489	Applicant(s) Tschopp
	Examiner Karen Canella	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 *months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *36-42* is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *36-42* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 3

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. Acknowledgment is made of applicants election with traverse of Group IX, drawn to methods of treating, suppressing or altering the progression of cancer, and methods for suppressing the growth of a tumor comprising administering an agent capable of blocking the association of APRIL ligand with its receptor. The traversal is on the grounds that the restriction is improper that 1) the examiner did not establish patentable distinctness by two criteria, as set forth in the MPEP, 2) Groups IV, V, VIII and XI have all been classified by the examiner as belonging to class 530, therefore there is no undue search burden, 3)Group V should not have been restricted from Group IX as both groups are drawn to methods of treating cancer by disrupting the interaction between APRIL and its receptor, 4)Groups VIII and IX should be examined together as both groups are drawn to methods of treatment depending on the disruption of the April-receptor interaction. This has been considered and found partially persuasive. After review of the specification and reconsideration of the restriction requirement, the examiner concludes that Group V and Group IX should be re-joined. However, the other traversals of the restriction requirement were not found persuasive. The MPEP states that although there are two criteria for the establishment of distinctness in the case of products and methods of use, either or both of the criteria need be fulfilled for the establishment of patentable distinctness. Therefore as the examiner cited other methods wherein the claimed products of Groups I-III can be used, the restriction between product and process of use was proper. Groups VIII, drawn to a method of inducing cell death and altering or activating an immune response, and Group IX, drawn to methods of treating, suppressing or altering the progression of cancer will not be joined as they have completely different method objectives and therefore require the consideration of different patentability issues. Further, Groups IV, V, VIII and XI will not be re-joined as classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Clearly different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is adhered to. The requirement is therefore made FINAL.

2. Claims 1-35 have been canceled. Claims 41 and 42 have been amended. Claims 36-42 are examined on the merits.

3. The amendment filed 4/13/01 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: amended claim 41, parts a, b and c and amended claim 42, parts a, b and c. There is no support in the specification for the specific fragments of SEQ ID NO:2 recited in the amended claims.

Applicant is required to cancel the new matter in the reply to this Office action.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 37 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The recitation of "an anti-APRIL receptor antibody" in claim 37 lacks proper antecedent basis in claim 36. Claim 36 is drawn to modified inhibitory form of APRIL and anti-APRIL antibodies.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 36-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 36-42 are drawn to methods of treating cancer in a patient comprising the administration of an agent which block the interaction between APRIL and its receptor. Further embodiments include a modified inhibitory form of APRIL or anti-APRIL antibodies as the agent. The specification teaches that a soluble recombinant protein consisting of the carboxyl terminal amino acids 110-250 of APRIL was demonstrated to increase cellular proliferation in Jurkat, Raji, and mouse A20 cells grown in culture. The specification further teaches that NIH 3T3 cells transfected with full length DNA encoding APRIL proliferated faster than mock-transfectants. However, the specification does not teach

a) specific tumors types that produce or overproduce APRIL as a soluble protein or have an APRIL receptor,

b) a specific agent such as an APRIL variant defined by amino acid sequence which can act as an antagonist in vivo at the APRIL receptor or an antibody which recognizes a specific epitope of APRIL or APRIL receptor which would be effective at blocking APRIL from interaction with its receptor when administered in vivo, or

c) the inhibition of malignant cell proliferation in vivo following the disruption of the April-receptor interaction.

(A)As drawn to specific tumor types and the presence of APRIL ligand and receptor.

The specification teaches that the 2.1 kb transcript of APRIL was found in normal colon, spleen and pancreas, two transcripts of 2.4 and 2.1 kb were found in the prostate and a transcript of 1.8 kb was found in peripheral blood leukocytes. The specification teaches the mRNA was found in many libraries derived from tumors such as ovary, prostate, Wilms, colon, endometrium, parathyroid, pancreas, and T-cell lymphoma. The specification does not teach that any of these tumors produces APRIL as a protein. Those of skill in the art, recognize that expression of mRNA does not dictate the translation of such mRNA into a polypeptide. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin

mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Thus, predictability of protein translation is not necessarily contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Therefore, one of skill in the art would not be able to predict if the mRNA found in the various tumor libraries were in fact translated into the APRIL polypeptide. Further, the specification provides no objective evidence that libraries derived from tumors such as ovary, prostate, Wilms, colon, endometrium, parathyroid, pancreas have a functional APRIL receptor and would be susceptible to the effects of APRIL ligand. In view of the above, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the claimed invention.

(B)As drawn to a specific APRIL antagonist, or antibody to APRIL or APRIL receptor.

Claims 36, 37, 39 and 40 are drawn in part to a method of treating cancer comprising the administration of a modified inhibitor form of APRIL effective for blocking the interaction between APRIL and its receptor. However the specification fails to specifically teach what this modified inhibitory form of the protein should consist of. The specification does not provide objective evidence of a fragment or mutant of SEQ ID NO:2 which could compete with the secreted or shed form of APRIL in an antagonistic or neutral manner, as the specification does not

teach regions of SEQ ID NO:2 which are responsible for the activation of the APRIL receptor. Therefore, one of skill in the art would be subject to undue experimentation to find fragments or mutants of SEQ ID NO:2 which would be effective in a method of treating cancer in a patient, as one of skill in the art would not be able to anticipate which specific regions of SEQ ID NO:2 should be deleted or altered. Further, claim 38 is drawn to an anti-APRIL receptor antibody. Firstly, the specification does not disclose the APRIL receptor. Secondly, if the APRIL receptor were disclosed, one of skill in the art would not be able to anticipate what epitopes of the receptor would generate antibodies which would have the property of blocking the interaction of the receptor with APRIL, in an antagonistic of neutral manner. Given the lack of guidance in the specification and the unpredictability in the art, one of skill in the art would be subject to undue experimentation in order to practice the claimed invention.

(C)As drawn to the inhibition of malignant cell proliferation in vivo

Claims 36-42 are drawn to a method of treating cancer in a patient by the disruption of the interaction between APRIL and the APRIL receptor. The claims thus encompass the inhibition of malignant cells in vivo. For the reasons given in parts (A) and (B) above, the specification is not enabling for the disruption of the interaction between APRIL and the APRIL receptor. The specification teaches that flag-tagged APRIL increases the number of Jurkat cells grown in culture relative to control cells. The specification teaches that an anti-flag antibody eliminated the flag-tagged APRIL from the conditioned medium and thus slowed down the cell growth. The specification did not teach a specific antibody to APRIL or APRIL receptor that could prevent the binding of free APRIL to its receptor in a manner which would inhibit the growth of a malignant cell. The specification provides no objective evidence that an exogenously administered antibody could kinetically compete with APRIL ligand, as APRIL ligand is a potential autocrine growth factor. The specification provides no evidence as to the turnover of the APRIL receptor or the length of time an APRIL ligand resides in a receptor. If the receptor ligand interaction is more than transient, the effectiveness of a competitor to free APRIL ligand will be severely limited. Further, the examples of growth stimulation by APRIL ligand given in the specification all involve cells grown in suspension culture or cells grown in a monolayer. One cannot extrapolate results

from such experimental systems to solid tumors in situ as variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. In addition, the formulation may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, it may be absorbed by fluids, cells and tissues where the formulation has no effect, the circulation into the target area may be insufficient to carry the formulation and a large enough local concentration may not be established. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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Patent Examiner, Group 1642
June 28, 2001

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